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GBV-C/Hepatitis G Virus in Acute nonA–E Hepatitis and in Acute Hepatitis of Defined Aetiology in Italy

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The role of GBV-C/HGV in the aetiology of acute non A–E hepatitis and its impact on the course of acute hepatitis of defined aetiology were investigated by detecting viral RNA by RT-PCR and antibody to the E2 protein of GB virus C (anti-E2) by EIA. Ninety-eight patients with acute nonA–E hepatitis, 35 patients with acute hepatitis A, 63 with acute hepatitis B, 29 with acute hepatitis C and 270 controls were enrolled in this study. The prevalence of GBV-C/HGV RNA was similar among patients with acute nonA–E hepatitis (3.1%), with acute hepatitis A (2.9%), and controls (3.7%), but significantly higher ($P < 0.05$) among those with hepatitis B or C (19.0% and 48.3%, respectively). Similar figures were obtained considering the total rate of GBV-C/HGV exposure (viral RNA or anti-E2 positivity). The majority (24/30 or 80%) of GBV-C/HGV RNA positive patients reported a parenteral source of exposure whereas the remaining 20% denied having known risk factors. The liver function test values and the rate of chronic hepatitis B and C were similar in patients co-infected and in those not co-infected with GBV-C/HGV. This study excludes a significant role of GBV-C/HGV infection in the aetiology of acute nonA–E hepatitis in Italy. Concomitant GBV-C/HGV and HBV or HCV infection does not worsen the clinical course of illness among patients with acute hepatitis. ***J. Med. Virol. 61:59–64, 2000.*** © 2000 Wiley-Liss, Inc.

KEY WORDS: GBV-C; acute hepatitis; nonA–E hepatitis

INTRODUCTION

Approximately 10% of patients with acute hepatitis reported annually in Italy, and 15% of those with chronic hepatitis are classified as non-A–D, because they are negative for all markers of replication associated with the major hepatotropic viruses (namely HAV, HBV, HCV, HDV) and have no other recognised sources of disease such as use of hepatotoxic drugs, alcohol or evidence of metabolic disorders or autoimmunity. These data, together with the occurrence of multiple bouts of hepatitis in some patients, provide both clinical and epidemiological evidence on the existence of one or more as yet unidentified hepatotropic viruses. In Italy, as in other industrialised countries, hepatitis E virus (HEV) is of minor importance, accounting for approximately 10% of acute nonA–C hepatitis, generally occurring in international travellers on return from endemic areas (Zanetti et al., 1999). A novel flavi-like virus, named GBV-C (Simons et al., 1995) has been identified in association with nonA–C hepatitis. Another group of investigators (Linnen et al., 1996) described another virus termed hepatitis G virus, also associated with nonA–C hepatitis cases. Hepatitis G virus (HGV) is a genotype of GBV-C (Muerhoff et al., 1996). Several studies failed to demonstrate any relationship between GBV-C/HGV infection and liver damage (Bralet et al., 1997; Francesconi et al., 1997; Thomas et al., 1997; Fabris et al., 1998). Other reports, however, demonstrated otherwise (Colombatto et al., 1996, 1997; Fiordalisi et al., 1996; Manolakopolus et al., 1998; Mushahwar and Zuckerman, 1998). The aim of this study was to evaluate the aetiological role of GBV-C/HGV infection in acute nonA–E hepatitis and to determine whether GBV-C/HGV plays an aetiological role with concomitant infection with hepatitis A virus (HAV), with hepatitis B virus (HBV) or hepatitis C virus (HCV).

MATERIALS AND METHODS

Study Population

Serum samples collected between January 1992 and December 1998 from 98 patients (60 males, 38 females,

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TABLE I. Rate of GBV-C/HGV Infection in Patients With Acute Hepatitis According to the Aetiology and in Healthy Controls

Aetiology	Number of cases	Gender M/F	Mean age (range)	GBV-C/HGV RNA+	anti-E2+	Total exposed
Hepatitis nonA–E	98	60/38	35.3 (8–70)	3 (3.1%)	23 (23.4%)	26 (26.5%)
Hepatitis A	35	23/12	30.8 (8–53)	1 (2.9%)	6 (17.1%)	7 (20%)
Hepatitis B	63	52/11	33.9 (19–70)	12 (19.0%)	18 (28.6%)	30 (47.6%)
Hepatitis C	29	17/12	29.3 (17–41)	14 (48.3%)	10 (34.5%)	24 (82.8%)
Controls	270	158/112	34.7 (18–54)	10 (3.7%)	42 (15.6%)	52 (19.3%)

mean age 35.3 years, range 8–70) with acute nonA–E hepatitis and from 127 patients (92 males, 35 females, mean age 32.1 years, range 8–70) with acute hepatitis of known aetiology: 35 (27.6%) with hepatitis A, 63 (49.6%) with hepatitis B, 29 (22.8%) with hepatitis C were examined for GBV-C/HGV RNA and anti-E2 antibody. The disease had a fulminant course in three patients (two with acute hepatitis B and one with acute nonA–E hepatitis) while the remaining patients displayed a gradual improvement in biochemical parameters. From each patient included in the study, several serum samples drawn during and after the acute phase of the disease, were collected and stored at minus 80°C before testing. As controls, 270 healthy individuals of comparable age (mean 34.7 years, range 18–54) and gender (158 males and 112 females) were enrolled. Informed consent was obtained from each person enrolled in the study.

Diagnosis of acute nonA–E hepatitis was made by the exclusion of the major hepatitis viruses (i.e., HAV, HBV, HCV, HDV, HEV) and also of other causes of liver damage such as drugs, alcohol and autoimmunity. Conversely, acute hepatitis of known aetiology was defined by the serological detection of one or more specific markers of acute viral hepatitis. In particular: acute hepatitis A was defined by the presence of IgM anti-HAV; hepatitis B by the presence of HBsAg and IgM anti-HBc; hepatitis delta by the detection of IgM anti-HDV; hepatitis C by the detection of HCV-RNA or seroconversion to anti-HCV and hepatitis E by the detection of HEV-RNA and anti-HEV of IgM class or seroconversion to anti-HEV of IgG class. All patients included in this study were HIV negative.

To identify risk factors for hepatitis during the six months preceding the onset of the illness, each patient was interviewed with a pre-coded questionnaire.

Laboratory

Commercially available enzyme immunoassays (EIA) were used to detect IgM anti-HAV, HBsAg, IgM anti-HBc, anti-HCV and anti-HEV (Abbott Laboratories, North Chicago, IL). HCV-RNA was assayed by RT-PCR with nested primers derived from the 5′-non coding region of the viral genome (Imberti et al., 1991). HEV-RNA was detected by RT-PCR with nested primers derived from the open reading frame 1 (ORF-1) of the genome of the original Burmese HEV strain (Schlauder et al., 1993). Anti-HEV of IgM class was assayed by an "in house" modified EIA, as previously reported (Zanetti et al., 1999).

GBV-C/HGV RNA was detected with the Abbott LCx® system and antibody to the envelope GBV-C/HGV glycoprotein (anti-E2) was assayed by EIA at Abbott Laboratories (Marshall et al., 1998; Zanetti et al., 1998). Anti-nuclear, anti-smooth muscle, liver kidney microsome autoantibodies were determined by indirect immunofluorescence. Liver function tests were carried out by routine methods.

Statistical Analysis

Differences in frequencies among the groups were compared by two-tailed Fisher's exact and Chi-square tests. Group means were compared by the Student's *t*-test. The Confidence Intervals (CI) at 95% were calculated by Fleiss quadratic method; for all results, upper and lower CI limits for 95% are given.

RESULTS

Prevalence and Significance of GBV-C/HGV in Patients With Acute Hepatitis

Age, gender and prevalence of exposure to GBV-C/HGV infection among patients with acute hepatitis of known and unknown aetiology and among controls are shown in Table I. The prevalence of GBV-C/HGV RNA was similar among patients identified as having acute nonA–E hepatitis (3.1%; CI 0.8–9.3%), acute hepatitis A (2.9%; CI 0.1–16.6%) and controls (3.7%; CI 1.9–6.9%) but significantly higher ($P < 0.05$) among patients with acute hepatitis B (19.0%; CI 10.6–31.3%) and among those with hepatitis C (48.3%; CI 29.9–67.1%). Similarly, the total of GBV-C/HGV exposure (presence of viral RNA plus anti-E2 antibody) was much higher ($P < 0.05$) among patients with acute hepatitis B (47.6%; CI 35–60.5%) or hepatitis C (82.8%; CI 63.5–93.5%) than among those with hepatitis A (20%; CI 9.1–37.5%), hepatitis nonA–E (26.5%; CI 18.3–36.6%) and controls (19.3%; CI 14.8–24.6%). In all patients, GBV-C/HGV RNA and anti-E2 antibody were mutually exclusive. The disease had a fulminant course in three patients (two with acute hepatitis B

TABLE II. Clinical and Biochemical Features of Patients With Acute Hepatitis According to the Aetiology and GBV-C/HGV RNA Status

	GBV-C/HGV RNA +	GBV-C/HGV RNA –	*P* value
Hepatitis nonA–E (n = 98)	3	95	
Mean age, years (range)	30.5 (27–34)	35.4 (1–79)	NS
Gender (M/F)	2/1	58/37	NS
ALT	1041.3 ± 958.4	1509 ± 1358.1	NS
Hepatitis A (n = 35)	1	34	
Mean age, years (range)	24	31.1 (8–53)	NA
Gender (M/F)	1/0	22/12	NA
ALT	1560	2365.8 ± 1156.9	NA
Hepatitis B (n = 63)	12	51	
Mean age, years (range)	30.5 (19–51)	34.3 (19–70)	NS
Gender (M/F)	10/2	42/9	NS
ALT	4008.6 ± 1512.5	3096 ± 1946.9	NS
Hepatitis C (n = 29)	14	15	
Mean age, years (range)	25.5 (17–31)	29.9 (17–41)	NS
Gender (M/F)	9/5	8/7	NS
ALT	1206.6 ± 460.1	1281.4 ± 558.6	NS

ALT values represent the mean peak values ± SD observed during hospital admission. NS, non significant; NA, not applicable. Normal ALT range ≤ 45 IU/l.

and one with acute nonA–E hepatitis), all of whom were negative for both GBV-C/HGV RNA and anti-E2 antibodies. All patients with acute hepatitis B were negative for delta markers. In Table II the demographic and clinical characteristics were compared on the basis of their GBV-C/HGV status. In all aetiological groups, the patients positive for GBV-C/HGV RNA were comparable with those without GBV-C/HGV regarding age, gender and ALT mean peak values. Also, no difference was found regarding mean levels of aspartate aminotransferase, gamma-glutamyl transpectidase, alkaline phosphatase and bilirubin levels (data not shown in table) among patients with and without GBV-C/HGV infection. In particular, all three patients with acute nonA–E hepatitis found GBV-C/HGV RNA positive had relatively mild acute illness with complete biochemical resolution of hepatitis within 3–5 weeks.

As for risk factors (Table III), 14 of the 30 (46.7%, CI 28.8–65.4%) patients found GBV-C/HGV positive were intravenous drug users, 7 (23.3%, CI 10.6–42.7%) were at high sexual behaviour risk, one (3.3%, CI 0.2–19.1%) had a history of blood transfusion, 2 (6.7%, CI 1.2–23.5%) had other parenteral exposures and 6 (20%, CI 8.4–39.1%) denied having at least one of the major risk factors.

Follow-Up

During the follow-up period, none of the patients with nonA–E acute hepatitis developed markers of HAV, HBV, HCV, or HEV infection. Despite complete recovery and normal ALT, GBV-C/HGV RNA persisted in two of three patients with acute nonA–E hepatitis after 9 and 18 months respectively, whereas the third patient lost viral RNA with seroconversion to anti-E2 antibody at the follow-up at 30 months after onset of the disease (Fig. 1).

Among patients with acute hepatitis A, B or C, the clinical outcome was not influenced apparently by the GBV-C/HGV RNA positivity. The rate of hepatitis C chronicization (demonstrated by the persistence of both HCV-RNA positivity for more than 6 months and ALT abnormality) was comparable among patients with or without GBV-C/HGV co-infection; in particular, the rate was 92.9% (13/14; CI 64.2–99.6%) in GBV-C/HGV RNA positive and 80% (12/15; CI 51.4–94.7%) in GBV-C/HGV RNA negative patients (*P* = non significant). Concerning hepatitis B, all 12 patients co-infected with GBV-C/HGV and 50 of the 51 (98%; CI 88.2–99.9%) with HBV alone recovered from hepatitis B with seroconversion to anti-HBs antibody. Again, despite continuing normal ALT, all 12 patients remained GBV-C/HGV RNA positive during the entire follow-up period (mean 3.2 months, range 9–80 months) (Fig. 2).

DISCUSSION

Despite the availability or reliable diagnostic tests, several cases of acute hepatitis remain unexplained, suggesting the existence of other unidentified infectious agents of human hepatitis. The discovery of GBV-C/HGV, a novel agent belonging to the flaviviridae family, raised hope that an important step had been made in the clarification of the aetiology of acute nonA–E hepatitis (Hadziyannis, 1997). The role of GBV-C/HGV in acute hepatitis of unknown aetiology, however, is far from complete. Therefore, we evaluated the prevalence, the clinical significance of GBV-C/HGV infection and related risk factors in 98 Italian patients with acute hepatitis nonA–E as well as in patients with acute hepatitis of defined aetiology and in healthy individuals. GBV-C/HGV was detectable only in 3.1% of patients with acute nonA–E hepatitis. This prevalence was similar to that found in patients with acute hepatitis A and in controls, but significantly lower than that found both in patients with acute hepatitis B and acute hepatitis C. A similar figure was also obtained considering the total of the exposed patients (GBV-C/HGV RNA plus anti-E2). These findings confirm that GBV-C/HGV does not represent an important aetiologic agent of nonA–E hepatitis and are in agreement with previous reports (Yashina et al., 1997; Fabris et al.,

TABLE III. Risk Factors Among 30 GBV-C/HGV Positive Patients With Acute Hepatitis of Known and Unknown Aetiology

Risk factors	Hepatitis A GBV-C/HGV RNA + (n = 1}	Hepatitis B GBV-C/HGV RNA + (n = 14)	Hepatitis C GBV-C/HGV RNA + (n = 14)	Hepatitis nonA–E GBV-C/HGV RNA + (n = 3)	Total GBV-C/HGV RNA + (n = 30)
Row shell fish	0	0	0	0	0
International travels	0	0	0	0	0
IVDU's	1 (100%)	4 (33.3%)	9 (64.3%)	0	14 (46.7%)
High risk sexual behaviour[a]	0	5 (41.7%)	2 (14.3%)	0	7 (23.3%)
Transfusions	0	0	1 (7.1%)	0	1 (3.3%)
Other parenteral exposures[b]	0	1 (8.3%)	0	1 (33.3%)	2 (6.7%)
Unknown	0	2 (16.7%)	2 (14.3%)	2 (66.7%)	6 (20%)

[a]This category includes sexual contacts with someone who had a history of hepatitis, homosexual and bisexual intercourses or multiple sexual partners.
[b]This category includes hospitalization, dental care, health-care workers, and needle-stick.

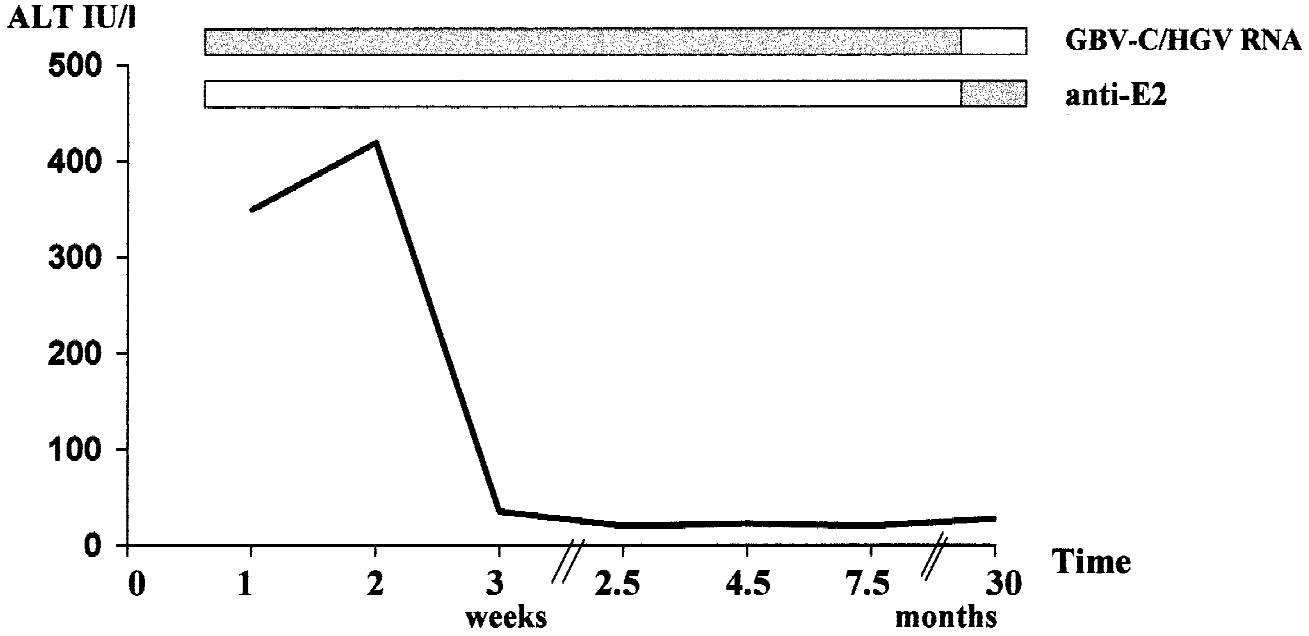

Fig. 1. Clinical course of a patient with acute nonA–E hepatitis infected with GBV-C/HGV.

1998). For the few cases with nonA–E hepatitis and GBV-C/HGV infection, because no marker of acute infection is available at present, a causative association of the virus with disease can be inferred but not clearly proven. The high frequency of GBV-C/HGV infection in patients with acute hepatitis B or C, especially intravenous drug abusers, confirms that this virus is transmitted mainly by parenteral routes, as demonstrated in studies carried out among haemodialysed and multitransfused patients (Masuko et al., 1996; Kinoshita et al., 1997). The stratification according to the risk factors showed that sexual contact may also be another important route of GBV-C/HGV transmission, supporting previous epidemiological observations among homosexual and bisexual men and the demonstration of the virus in the semen of infected men (Stark et al., 1996; Semprini et al., 1998). It has been demonstrated that the combined HCV and GBV-C/HGV co-infections were no more severe than HCV infections alone, and that the ALT values paralleled the levels of HCV RNA but not those of GBV-C/HGV RNA (Tanaka et al., 1996). Our data are in agreement with these previous reports confirming that GBV-C/HGV co-infection did not worsen the clinical course of acute illness among patients with acute hepatitis B or C and had no apparent influence on the rate of chronicization and severity of chronic disease (Alter et al., 1997). Furthermore, the demonstration that GBV-C/HGV RNA persists in the sera for long periods without biochemical evidence of liver damage either in patients who recovered from acute hepatitis B or in patients with GBV-C/HGV infection alone, suggests that this virus is not primarily a

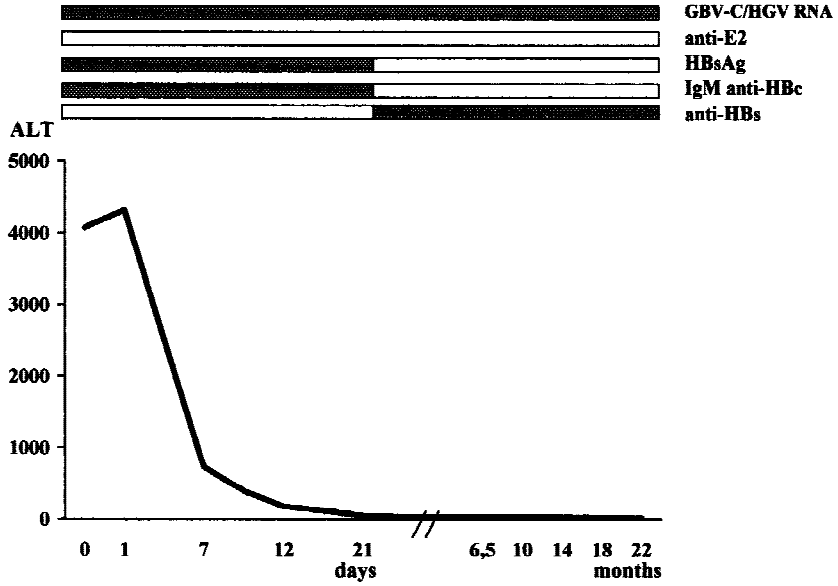

Fig. 2. Clinical course of a patient with acute hepatitis type B co-infected with GBV-C/HGV.

hepatotropic agent. In conclusion, the data demonstrate that GBV-C/HGV does not represent an important causative agent of acute nonA–E hepatitis in Italy. In addition, GBV-C/HGV co-infection does not worsen the clinical course of illness among patients with acute hepatitis of defined aetiology.

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